



PATENT  
071949-2406 (formerly 234/116)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Buechler, *et al.*

Serial No.: 09/066,255

Title: HYBRID PHTHALOCYANINE  
DERIVATIVES AND THEIR USES

Filing Date: April 23, 1998

Group Art Unit: 1627

Examiner: Garcia, M.

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APPEAL BRIEF

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Applicants (herein, "Appellants") hereby appeal the Final Rejection of claims 28, 30, 32 and 34. This Appeal Brief is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(f). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit our Deposit Account No. 50-0872 (Order No. 071949-2406) for the appropriate amount.

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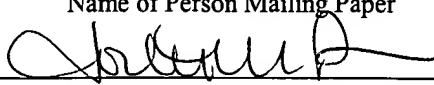
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***Real Party in Interest***

The real party in interest in this appeal is Biosite Diagnostics, Inc., which is the assignee of the present application.

***Related Appeals and Interferences***

Appellants are not aware of any related appeals or interferences that may have a bearing on the board's decision in the pending appeal.

***Status of Claims***

On July 9, 2001, Appellants Notice of Appeal from the Examiner's Action of April 4, 2001, making final the rejection of claims 28, 30, 32 and 34, was entered. These claims stand finally rejected under 35 U.S.C. § 112, second paragraph and 35 U.S.C. §103.

***Status of Amendments***

No amendments remain outstanding in the application.

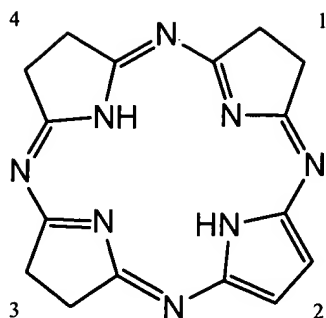
***Summary of The Invention***

The present invention relates in part to assay methods that utilize water soluble hybrid phthalocyanine derivatives as fluorescent labels. The water soluble hybrid phthalocyanine derivatives of the instant invention exhibit advantageously large stokes shifts and intensities, and are useful as labels, for example in assays for determining the presence or amount of an analyte in aqueous samples.

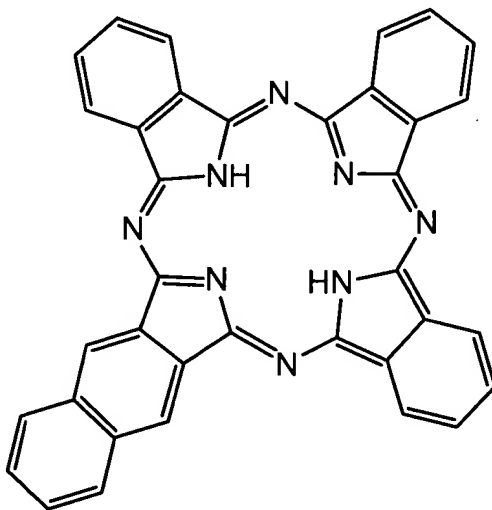
At the time the instant application was filed, methods for detecting analytes -- commonly referred to as a "target ligand" -- in fluid samples, and particularly biological samples, were well known to those of skill in the art. Numerous detectable labels, including fluorescent labels, had been used to provide a detectable signal in these methods. The term "fluorescence" refers to the property of absorbing incident light at one wavelength, and emitting light at a second, longer, wavelength in response.

When such assays depend upon fluorescent labels, the characteristics of both the fluorescent label and the sample must be considered to provide the desired sensitivity to the assay. For example, (1) the absorption (or "excitation") and emission wavelengths of the label should not correspond closely to the absorption or fluorescence of the sample; (2) the difference between the excitation and emission wavelengths of the label (the "stokes shift") should be as large as possible to minimize the background signal resulting from detection of the excitation light source; (3) the dye must be compatible with the fluid phase of the assay; that is, the dye must be water soluble or water insoluble depending on the solvent used in the assay; and (4) the dye should be as bright as is necessary to achieve the desired sensitivity.

The instant invention provides methods in which water soluble hybrid phthalocyanine derivatives are used as fluorescent labels for measuring target ligands in biological samples. Hybrid phthalocyanine derivatives are molecules comprising a base ring of four pyrrole moieties, known as a "tetraazapyrrole" structure:



As described in the instant claims, hybrid phthalocyanine derivatives are those in which one of the four pyrrole moieties are fused to a single carbocyclic ring, each of the other three are fused to from zero to three carbocyclic rings, and at least two of the four pyrrole moieties are fused to a different number of rings. The following is an example of a typical hybrid phthalocyanine derivative:



The present invention describes for the first time that such molecules exhibit fluorescent properties that render them particularly useful in assays for target ligands in fluid samples. For example, the water soluble hybrid phthalocyanine derivatives of the instant claims can provide

large stokes shifts (in excess of 100 nm), and may be tuned to wavelengths that are compatible with the absorption and emission of the sample, for example, blood, serum, plasma, urine, ground water, and the like. Additionally, because the hybrid phthalocyanine derivatives are water soluble, they may be easily used for labeling molecules, proteins, nucleic acids or cells.

***Issues***

1. Whether the term “ligand analogue” used in the rejected claims is indefinite within the meaning of 35 U.S.C. §112, second paragraph, when the term is well known and commonly used by those of skill in the art, and when the instant specification and file history define the term consistently with its common usage.
2. Whether claims to methods for determining the presence or amount of at least one target ligand in a fluid sample, using a ligand analogue coupled to a signal development element comprising a water soluble hybrid phthalocyanine derivative, in which the hybrid phthalocyanine derivatives have a precisely defined structure, are obvious over a combination of publications which do not disclose that water soluble hybrid phthalocyanine derivatives have any fluorescent properties whatsoever, and when the alleged “advantages” on which the Examiner relies in support of the asserted prima facie case relate solely to the use of phthalocyanine derivatives in phototherapy, and not to their use as labels in an assay to determine the presence or amount of a target ligand.



***Grouping of Claims***

Claims 28, 30, 32 and 34 stand or fall together.

***The Examiner's Rationale***

The Examiner's rationale for rejecting claims 28, 30, 32 and 34 can be found in the Office Action, made final, mailed on April 4, 2001 ("Paper No. 12"), and the Advisory Action mailed on July 25, 2001 ("Paper No. 16").

1. 35 U.S.C. §112, second paragraph, rejection

The Examiner contends that the term "ligand analogue" used in the instant claims is allegedly indefinite. In particular, the Examiner asserts "it is not clear what the similarities and differences between the ligand and the ligand analogue." Paper No. 16, page 2.

2. 35 U.S.C. §103 rejection

The Examiner contends that the claims are allegedly unpatentable over Margaron *et al.*, *J. Photochem. Photobiol. B* 14: 187-99 (1992), in view of Renzoni *et al.*, U.S. Patent No. 5,135,717.

In supporting the purported *prima facie* case of obviousness, the Examiner states that the Margaron *et al.* publication discloses water-soluble hybrid phthalocyanine derivatives, and that such molecules allegedly have "superior absorption properties" because they absorb light toward the red end of the spectrum, permitting the use of "less expensive and more reliable light sources for such wavelengths." Paper No. 16, page 3. The Examiner does not contend that the Margaron

*et al.* publication discloses the use of water-soluble hybrid phthalocyanine derivatives in analyte assays, such as those of the instant claimed.

The Examiner argues, however, that the Renzoni *et al.* publication discloses non-hybrid phthalocyanine “useful as *fluorescent reporting groups*, imaging agents and also as *therapeutic agents*.” Paper No. 6, page 4 (emphasis in original). The Examiner contends that it would have been obvious to use the water-soluble hybrid phthalocyanine derivatives disclosed by the Margaron *et al.* publication in the fluorescent conjugates disclosed by the Renzoni *et al.* publication because of the alleged “superior absorption properties” discussed above. Additionally, the Examiner contends that one would expect the water-soluble hybrid phthalocyanine derivatives disclosed by the Margaron *et al.* publication to have suitable fluorescence properties because “it is well known in the art that phthalocyanine derivatives are fluorescent” and hybrid phthalocyanine derivatives allegedly “possess a high degree of structural similarity.” Paper No. 16, page 5-6.

### ***Argument***

1. Appellants respectfully submit that the instant claims meet the definiteness standard of 35 U.S.C. §112, second paragraph with regard to the phrase “ligand analogue.” This phrase is well known and commonly used by the skilled artisan. Moreover, the phrase has been defined by Appellants in both the instant specification and file history consistently with this common usage. Appellants, therefore, respectfully request that the rejection of claims 28, 30, 32 and 34 under 35 U.S.C. §112, second paragraph, be withdrawn or reversed.

2. Additionally, Appellants respectfully submit that the instant claims are not obvious in view of the publications cited by the Examiner. The cited references, alone or in combination, do not disclose or suggest that water soluble hybrid phthalocyanine derivatives have any fluorescent properties whatsoever, much less fluorescent properties that would render them suitable in the instantly claimed analyte assays. Moreover, the alleged “superior absorption properties” that the Examiner cites as “advantages” in support of the asserted *prima facie* case relate solely to the use of phthalocyanine derivatives in phototherapy, and not to their use as labels in an analyte assay. Appellants, therefore, respectfully request that the rejection of claims 28, 30, 32 and 34 under 35 U.S.C. §103 be withdrawn or reversed.

1. 35 U.S.C. §112, Second Paragraph

In contradiction to the Examiner’s contention that the phrase “ligand analogue” is allegedly indefinite, the phrase is both well known to those of ordinary skill in the art, and defined in the instant specification and file history. Thus, because the skilled artisan is reasonably apprised of the meaning of this phrase, the claims meet the standard of 35 U.S.C. §112, second paragraph.

*Applicable Legal Standard*

When determining definiteness, the proper standard to be applied is “whether one skilled in the art would understand the bounds of the claim when read in the light of the specification.” *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). *See also, Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) (“If the claims read in the light of the

specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.”) (emphasis added). *See also*, MPEP §2173.02 (An examiner “should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.”) (emphasis in original).

*The phrase “ligand analogue” is well known and commonly used by those of skill in the art*

The Examiner contends that the phrase “ligand analogue” allegedly makes it impossible to determine the metes and bounds of the invention, because “it is unclear what are the similarities and differences between the ligand and the ligand analogue.” Paper No. 16, page 2. However, the Examiner’s contention is at odds with the common definition and use of the phrase by those of ordinary skill in the art.

For example, the skilled artisan is informed of the metes and bounds of the phrase “ligand analogue” by simply referring to common dictionary sources. Thus, the Dictionary of Cell Biology, Second Edition, Academic Press, San Diego, defines a “ligand” as “any molecule that binds to another”; and Merriam Webster’s Collegiate Dictionary, 10<sup>th</sup> Edition, defines an “analogue” as a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group.”

By these simple definitions, the skilled artisan would understand and acknowledge that the phrase “ligand analogue” in the instant claims refers to molecules that are capable of binding to a binding partner (*i.e.* ligand receptor) for a target ligand, but that may differ slightly in composition from the target ligand. Thus, the phrase “ligand analogue” is a functional expression

that refers to the binding characteristics of the ligand analogue in comparison to that of the target ligand.

Furthermore, this meaning of the phrase is confirmed by reference to the use of the phrase by those of ordinary skill in the art. For example, in describing a type of analyte assay, U.S. Patent No. 5,391,483 states “[i]n competitive binding assays, a labeled ligand analog... is placed in competition with the unlabeled ligand for reaction with a fixed amount of the appropriate binding material.” U.S. Patent No. 5,391,483, column 1, lines 29-33. Similarly, U.S. Patent No. 5,143,852 states [h]eterogeneous, competitive ligand-receptor assays require a separation of ligand analogue conjugate bound to a ligand receptor from the free ligand analogue conjugate and measurement of either the bound or the free fractions.” U.S. Patent No. 5,143,852, column 2, lines 21-29. Only a desire for brevity prevents additional citations of usage of the term by those of skill in the art.

These quoted passages use the phrase “ligand analogue” in precisely the functional manner discussed above. Moreover, the skilled artisan can easily determine whether a given molecule meets this definition by simply determining if the molecule is capable of binding to a ligand receptor. The Examiner has not indicated why, in the face of this common definition and usage, the skilled artisan would not be reasonably apprised of the meaning of the phrase. Instead, the Examiner simply asserts that “[t]he terminology... simply does not provide a standard for ascertaining the requisite degree of ‘analogy’ the applicant intends.” Paper No. 16, page 2. The Examiner’s assertion, however, does not comport with the reasonableness standard in 35 U.S.C. §112, second paragraph made explicit by the Court of Appeals for the Federal Circuit.

*The phrase “ligand analogue” has been defined consistently with this common usage by Appellants during prosecution*

Furthermore, both the instant specification and the file history make it clear that the phrase is used in the claims consistently with this definition. In particular, in the responses filed on July 5, 2001 and January 8, 2001, Appellants explicitly defined the phrase “ligand analogue” to refer to molecules that are capable of binding to a binding partner (*i.e.* ligand receptor) for a target ligand, but that may differ slightly in composition from the target ligand. Thus, the skilled artisan will understand that “ligand analogue” is a chemical compound that is structurally similar to a ligand but that may differ slightly in composition, and that is capable of binding to a binding partner (*i.e.* ligand receptor) for a target ligand. *See, e.g., Hormone Research Foundation, Inc. v. Genentech, Inc.*, 15 USPQ2d 1039 (Fed. Cir. 1990) (an applicant may be his or her own lexicographer, and may use terms even in a manner inconsistent with an ordinary meaning of the term, so long as that definition is made clear in the file history).

Accordingly, because the skilled artisan is reasonably apprised of the metes and bounds of the claims regarding the phrase “ligand analogue” the instant claims meet the requirements of 35 U.S.C. § 112, second paragraph. Appellants, therefore, request that the rejection be withdrawn or reversed.

2. 35 U.S.C. §103

In contradiction to the Examiner’s contentions, the skilled artisan would lack a motivation to combine the publications as suggested by the Examiner, because the cited

references do not disclose or suggest that water soluble hybrid phthalocyanine derivatives have any fluorescent properties whatsoever, much less fluorescent properties that would render them suitable in the instantly claimed analyte assays. Additionally, the alleged “superior absorption properties” that the Examiner cites as “advantages” in support of the asserted *prima facie* case relate to the use of phthalocyanine derivatives in phototherapy, or otherwise would not motivate the skilled artisan to combine the publications to provide the claimed assays for a target ligand. Therefore, the instant claims are not obvious in view of over Margaron *et al.*, *J. Photochem. Photobiol. B* 14: 187-99 (1992), in view of Renzoni *et al.*, U.S. Patent No. 5,135,717.

*Applicable Legal Standard*

To *establish* a *prima facie* case of obviousness, three criteria must be met; there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and the publications must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); *See also* MPEP § 2143.

*The “superior properties” of water soluble hybrid phthalocyanine derivatives on which the Examiner relies to combine the cited references fail to provide a motivation to provide the instantly claimed methods*

The Examiner cites the Margaron *et al.* publication as allegedly disclosing water soluble hybrid phthalocyanine derivatives, but acknowledges that the Margaron *et al.* publication, which is related solely to photodynamic therapy, does not disclose the use of water soluble hybrid

phthalocyanine derivatives as labels in assay methods. The Examiner's asserted *prima facie* case of obviousness seeks to combine the molecules disclosed in the Margaron *et al.* publication with the Renzoni *et al.* publication, which discloses the use of symmetrical (hence non-hybrid) phthalocyanine derivatives as labels in assays. Specifically, the Examiner contends that the Margaron *et al.* publication discloses that water soluble hybrid phthalocyanine derivatives exhibit alleged "advantages" that would motivate the skilled artisan to use such molecules as labels.

The first of these alleged "advantages" to which the Examiner refers, however, is related to the field of cancer phototherapy, and not to the use of hybrid phthalocyanine derivatives in labeled conjugates for assay methods. The Examiner states that the Margaron *et al.* publication discloses that "absorption [of light] above 680 nm is preferred" and that the molecules disclosed by the Margaron *et al.* publication can provide such absorption properties. Paper No. 16, page 3.

But the Examiner ignores the fact that this property is said to be "superior" because of the ability of light at that wavelength to penetrate deeper into tissues during photodynamic therapy, a consideration that is irrelevant to the instant claims. *See, e.g.,* Margaron *et al.*, page 188, first incomplete paragraph. The Examiner does not explain why the ability of light to penetrate deeper into tissues during cancer phototherapy would provide any motivation to the skilled artisan to use the molecules disclosed by the Margaron *et al.* publication in the instantly claimed analyte assays.

The second of the alleged "advantages" to which the Examiner refers is the ability to use "less expensive and more reliable light sources" with dyes absorbing above 680 nm. The Examiner contends that this provides "a beneficial result" supporting the combination of the



molecules disclosed in the Margaron *et al.* publication with the methods disclosed by the Renzoni *et al.* patent. But there are flaws in the Examiner's asserted *prima facie* case. The instant claims relate to methods that use water soluble hybrid phthalocyanine derivatives as fluorescent labels in assays, and there is nothing in the publications cited by the Examiner that would indicate that water soluble hybrid phthalocyanine derivatives would have any utility as a label, fluorescent or otherwise. Instead, the only use ascribed to these molecules is as a photosynthesizer in photodynamic therapy. Without Appellants' disclosure, indicating that water soluble hybrid phthalocyanine derivatives have advantageous fluorescent properties, the skilled artisan would lack a motivation to combine the references as suggested by the Examiner.

*The fact that both hybrid and non-hybrid phthalocyanine derivatives are useful in photodynamic therapy does not provide a motivation to use water soluble hybrid phthalocyanine derivatives in the claimed methods that are unrelated to photodynamic therapy*

In response to Appellants' remarks pointing out this flaw in the asserted *prima facie* case, the Examiner argues that the Margaron *et al.* publication allegedly discloses that water soluble hybrid phthalocyanine derivatives are useful in photodynamic therapy, and the Renzoni *et al.* patent discloses that non-hybrid phthalocyanine derivatives are also useful in photodynamic therapy. The Examiner then argues in reverse that, because the Renzoni *et al.* patent discloses that non-hybrid phthalocyanine derivatives are useful as labels, the skilled artisan would assume that hybrid phthalocyanine derivatives are also useful as labels. This leap of illogic ignores the fact that the characteristics of a molecule that is useful in photodynamic therapy are completely unrelated to the characteristics of a molecule that is useful as a detectable label.

For example, as noted by Kudrevich *et al.*, *J. Chem. Soc. Perkin Trans. 1* 1994: 2767-74, page 2767, left column, photodynamic therapy relies on the absorption of light by a photosynthesizer at a tumor site, resulting in generation of cytotoxic species such as singlet oxygen. The generation of cytotoxic species is unrelated to the ability of such a photosynthesizer to act as a fluorescent label in an assay for a target ligand. The mere fact that one type of molecule may be used as both a photosynthesizer and a label would not lead the skilled artisan to believe that all photosynthesizers would make a useful label. Moreover, the Examiner has provided no sound scientific principle on which to base such a conclusion. *See, e.g., In re Grose*, 201 USPQ 57 (CCPA 1979) (if the examiner is relying on a scientific theory to support an obviousness rejection, evidentiary support for that theory must be provided).

The Examiner also argues that the skilled artisan would assume that water soluble hybrid phthalocyanine derivatives are useful as labels because of an alleged “high degree of structural similarity” to non-hybrid phthalocyanine derivatives. This argument of “structural similarity,” however, is based simply on the Examiner’s assertion of similarity, and not on any sound scientific principle. As noted in the Renzoni *et al.* patent, even very simple changes to a non-hybrid phthalocyanine molecule, such as the addition of a coordinated cobalt or copper atom, can result in nonfluorescent molecules, while metal-free molecules cannot be rendered water soluble. *See, e.g., Renzoni et al.*, column 2, lines 1-18. Viewed without the benefit of Appellants’ disclosure, the skilled artisan would have considered the electronic differences between the water soluble hybrid phthalocyanine macrocycle as compared to non-hybrid molecules sufficient to render their fluorescence properties unpredictable. In the face of such unpredictability, the skilled

artisan would lack both a motivation and a reasonable expectation of success in combining the cited references as suggested by the Examiner. *See, e.g., In re Rinehart*, 189 USPQ 143 (CCPA 1976) (some degree of predictability is required to support a *prima facie* case of obviousness).

*Because the cited publications fail to indicate that water soluble hybrid phthalocyanine derivatives exhibit useful fluorescence properties, the Examiner's asserted prima facie case of obviousness must fall*

The Examiner attempts to dismiss Appellants' arguments that the cited references cannot support a *prima facie* case of obviousness by arguing that "the fluorescence properties of the hybrid phthalocyanine derivative(s) are... not being claimed. Paper No. 16, page 5. Here the Examiner ignores the requirements of the Examiner's own asserted *prima facie* case. There must be a motivation to the skilled artisan to combine the water soluble hybrid phthalocyanine derivatives allegedly disclosed by the Margaron *et al.* publication with the assays allegedly disclosed by the Renzoni *et al.* patent, thus providing the instantly claimed methods in which water soluble hybrid phthalocyanine derivatives function as detectable labels.

The alleged motivation must stem from the use by the Renzoni *et al.* patent of non-hybrid phthalocyanine derivatives as "fluorescent reporting groups," because fluorescence is the means by which such molecules generate a signal in an assay. Renzoni *et al.*, column 1, lines 17-25. Indeed, the Examiner goes so far as to highlight the Renzoni *et al.* patent's discussion of "fluorescent reporting groups." Paper No. 16, page 1. Thus, because there is nothing in the publications cited by the Examiner that would indicate that water soluble hybrid phthalocyanine

derivatives would have any utility as a fluorescent label, no motivation to combine the publications has been provided by the Examiner.

Similarly, the Examiner attempts to dismiss Appellants' arguments by stating that "the compounds of the Margaron *et al.* reference meet all of the limitations of the 'water-soluble hybrid phthalocyanine derivatives' of the claims and thus would have the same properties of such compounds. The fluorescence properties of such molecules are intrinsic in the molecule itself." Paper No. 16, page 4. This, however, ignores the fact that the Margaron *et al.* publication must be combined with additional references in order to "meet all of the limitations" of the instant method claims, and that, without some motivation to combine, a *prima facie* case of obviousness is not established. The fact that Appellants discovered that water soluble hybrid phthalocyanine derivatives can be used as fluorescent labels does not cure the fact that the Examiner has established no motivation to combine the Margaron *et al.* publication with the Renzoni *et al.* patent. *See, e.g., In re Vaeck*, 20 USPQ2d 1438 (the suggestion to combine the cited references and the reasonable expectation of success must come from the prior art, and not from applicant's disclosure).

*The Examiner has Fallen Victim To Impermissible Hindsight*

Appellants respectfully submit that, instead of carrying the burden of establishing a *prima facie* case of obviousness, the Examiner has fallen victim to "...decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming that it is easy to reassemble these elements into the invention...". *In re Mahurkar*, 28 USPQ2d 1801, 1817 (N.D.

Ill. 1993). An obviousness determination cannot be premised on such an impermissible use of hindsight. *See, In re Fine*, 5 USPQ2d 1596 1600 (Fed. Cir. 1988) (“To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.”)

*Even if a prima facie case of obviousness has been established, the superior properties of the instant invention rebut that prima facie case*

Finally, Appellants also respectfully submit that, even if a *prima facie* case of obviousness has been established, the superior and unexpected properties of the instant claims rebut that *prima facie* case. The water-soluble hybrid phthalocyanine derivatives of the instantly claimed methods exhibit advantageously large stokes shifts and intensities, as demonstrated by the instant specification, *e.g.*, in Table 2 beginning on page 85. Appellants have provided data in the specification which show that the water-soluble hybrid phthalocyanine derivatives of the instant claims exhibit Stokes shifts in excess of 100 nm (compared to the non-hybrid phthalocyanines disclosed in the Renzoni *et al.* patent, which have Stokes shifts of at most 47 nm, and more commonly less than 15 nm).

These advantageously large stokes shifts (more than double even the best dyes disclosed in the cited publications) result from the fact that the hybrid molecules appear to excite at the lowest absorbing subunit, and emit at the highest emitting subunit in the molecule, a fact which was unknown prior to Applicant's disclosure. *See, e.g.*, specification, page 33, lines 11-16.

Therefore, these unexpected advantageous properties of the water-soluble hybrid phthalocyanine

derivatives of the instantly claimed methods rebut any *prima facie* case the Examiner may have established.

In response to this argument, the Examiner again argues that “the compounds of the Margaron *et al.* reference meet all of the limitations of the ‘water-soluble hybrid phthalocyanine derivatives’ of the claims and thus would have the same properties of such compounds. The fluorescence properties of such molecules are intrinsic in the molecule itself.” Paper No. 16, page 4. But, again, the Examiner ignores the fact that all fluorescent properties of water-soluble hybrid phthalocyanine derivatives were unappreciated by the cited publications. The fact that hybrid molecules appear to excite at the lowest absorbing subunit, and emit at the highest emitting subunit in the molecule was completely unexpected and unpredicted by the cited references, rendering the use of hybrid molecules as labels in assays nonobvious.

Moreover, The Examiner has not explained why the use of “other hybrid phthalocyanine derivatives” in methods that are completely unrelated to the instantly claimed methods would be considered by the skilled artisan to represent the closest prior art, as the Examiner contends. Paper No. 16, page 6. Because only non-hybrid phthalocyanine molecules were understood to be useful as labels in assays prior to Appellants’ disclosure, the evidence of unexpected properties provided in the instant specification has been properly compared to non-hybrid phthalocyanine molecules, *i.e.*, the closest prior art. *In re Boesch*, 205 USPQ 215 (CCPA 1980). Thus, when properly considered, it is apparent that the superior and unexpected properties of water soluble hybrid phthalocyanine derivatives when used in the instantly claimed methods rebut any *prima facie* case of obviousness the Examiner may have established.

Because there is no motivation provided to combine the references cited by the Examiner, and no reasonable expectation of success in doing so, no *prima facie* case of obviousness has been established. Furthermore, even if a *prima facie* case of obviousness has been established, the superior properties of the instant invention rebut that *prima facie* case. Accordingly, the Examiner has failed to carry the burden of establishing a *prima facie* case of obviousness. Appellants, therefore, respectfully request that the rejection under 35 U.S.C. §103 be withdrawn or reversed.

***Conclusion***

For the reasons discussed above, the instant claims are in condition for allowance, and Appellants respectfully request that the rejections be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,  
FOLEY & LARDNER

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By: Michael A. Whittaker  
Michael A. Whittaker  
Registration No. 46,230

P.O. Box 80278  
San Diego, CA 92138-0278  
Telephone: (858)-847-6721  
Facsimile: (858) 792-6773



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*Appendix A: Text of the Claims Involved in the Appeal*

28. A method for determining the presence or amount of at least one target ligand in a fluid sample, the method comprising:

- a. contacting a fluid sample suspected of containing said target ligand with a ligand analogue conjugate and a ligand receptor, said ligand analogue conjugate comprising at least one ligand analogue coupled to a signal development element comprising a water soluble hybrid phthalocyanine derivative, to form a homogeneous reaction mixture, whereby said ligand analogue conjugate competes with said target ligand for binding to said ligand receptor, wherein said water soluble hybrid phthalocyanine derivative is a tetraazapyrrole molecule, wherein (i) at least one of the four pyrrole moieties is fused to a single carbocyclic ring to form a phthalocyanine subunit, (ii) each of the other three pyrrole moieties is fused to between zero and three carbocyclic rings to form a subunit selected from the group consisting of an azaporphine subunit, a phthalocyanine subunit, a naphthalocyanine subunit and an anthranylocyanine subunit, and (iii) at least two of the four pyrrole moieties comprises a different number of carbocyclic rings fused thereto;
- b. generating a detectable signal from ligand analogue conjugate bound to said ligand receptor in said reaction mixture; and
- c. relating the detectable signal to the presence or amount of said target ligand in said fluid sample.

30. A method for determining the presence or amount of at least one target ligand in a fluid sample, the method comprising:

- a. contacting said fluid sample suspected of containing said target ligand with a ligand analogue conjugate and a ligand receptor, said ligand analogue conjugate comprising at least one ligand analogue coupled to a signal development element comprising a water soluble



hybrid phthalocyanine derivative, to form a homogeneous reaction mixture, whereby said ligand analogue conjugate competes with said target ligand for binding to said ligand receptor, wherein said water soluble hybrid phthalocyanine derivative is a tetraazapyrrole molecule, wherein (i) at least one of the four pyrrole moieties is fused to a single carbocyclic ring to form a phthalocyanine subunit, (ii) each of the other three pyrrole moiety is fused to between zero and three carbocyclic rings to form a subunit selected from the group consisting of an azaporphine subunit, a phthalocyanine subunit, a naphthalocyanine subunit and an anthranylocyanine subunit, and (iii) at least two of the four pyrrole moieties comprises a different number of carbocyclic rings fused thereto;

b. generating a detectable signal from ligand analogue conjugate that is not bound to said ligand receptor in said reaction mixture; and

c. relating the detectable signal to the presence or amount of said target ligand in said fluid sample.

32. The method of claim 28, wherein said ligand analogue conjugate bound to said ligand receptor is bound to a solid phase prior to generating a detectable signal therefrom.

34. The method of claim 30, wherein said ligand analogue conjugate that is not bound to said ligand receptor is bound to a solid phase prior to generating a detectable signal therefrom.